REMARKS

Applicants have studied the Office Action mailed June 30, 2003. It is respectfully submitted that the application is in condition for allowance. Reconsideration and allowance of the pending claims in view of the following remarks is respectfully requested.

Rejection of claims 4, 8-9, and 24-29 under 35 USC §101 and §112, 1st paragraph:

The Examiner has rejected claims 4, 8-9, and 24-29 under 35 U.S.C.§101 and §112, 1st paragraph. In summary, the Examiner has stated that the claimed invention is not supported by either a substantial asserted utility or a well-established utility and, consequently, one skilled in the art would not know how to use the claimed invention.

In making these rejections, the Examiner states that there is no nexus between the claimed protein and therapeutics for humans, and that the specification as filed does not disclose or provide evidence that points to a property of the claimed protein such that another non-asserted utility would be established. The Examiner states that the polypeptide lacks substantial utility because further research to identify or reasonably confirm a "real world" context of use is required and, thus, the asserted utility lacks substantial and specific utility because further research to identify or reasonably confirm a "real world" context of use is required. The Examiner further asserts that the polypeptides do not (have) substantial utility because the skilled artisan would need to prepare, isolate, and analyze the protein in order to determine its functional nexus with human therapeutics. The Examiner states that, therefore, the invention is not in readily available form. Instead, further experimentation of the protein itself would be required before it could be used. The Examiner further states that the disclosed use for the nucleic acid molecule of the claimed invention is generally applicable to any nucleic acid and therefore is not particular to the nucleic acid sequence claimed.

Applicants respectfully traverse this rejection based on the following remarks.

Contrary to the Examiner's assertions, the claimed isolated nucleic acid molecules, such as SEQ ID NOS:1 and 3, that encode a specified amino acid sequence, SEQ ID NO:2, and methods of using such nucleic acid molecules have several uses that meet the requirements of 35 U.S.C.§101 and the first paragraph of 35 U.S.C.§112. These, as well as the accepted state of the art view that such molecules have uses within the commercial marketplace in the drug

development cycle, since they encode previously unidentified members of important pharmaceutical targets, establishes the utility of the claimed invention.

The utility requirement of a claimed invention requires that an invention must have a specific, substantial and credible utility. These requirements are defined in broad terms in cases such as *Brenner v. Manson*, 148 USPQ 689 (S. Ct. 1966) and the Utility Guidelines from the USPTO.

However, the notion that a recognized valuable addition to even entry points of the drug discovery cycle advances the art sufficient to establish a "usefulness" of a claimed invention should not be ignored. This is supported by previous case law (e.g., *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980)). Accordingly, the present invention, which is drawn to isolated nucleic acid molecules that encode a novel nuclear hormone receptor (SEQ ID NO:2), has valuable commercial utilities in the drug discovery process by providing previously unidentified members of an important pharmaceutical target class. The present invention provides sufficient knowledge and information that is beneficial to the public, and provides sufficient guidance for researchers to use the claimed subject matter to develop disease treatments and/or diagnostics. It is well recognized that nuclear hormone receptors are among the most important target for drug action (see, e.g., pages 1-12 of the specification). The public disclosure of a new member of the nuclear hormone receptor family through the patenting process clearly advances the art and augments the capabilities of biomedical researchers to combat illnesses.

The utility rejection raised by the Examiner also conflicts with the case *Juicy Whip v. Orange Bang* (Fed. Cir. 1999). *Juicy Whip* held that, in order to violate the utility requirement, an invention must be "totally incapable of achieving a useful result." The polypeptides and encoding nucleic acid molecules of the present invention are well known in the art to be valuable drug targets and therefore have readily apparent commercial utilities, such as for screening potential drug compounds, producing antibodies, developing hybridization probes and primers, etc. Therefore, the present invention is not "totally incapable of achieving a useful result." Instead, it is useful.

Applicants have provided sufficient guidance such that undue experimentation would not be required for one of ordinary skill in the art to comprehend the function and biological significance of the disclosed polypeptides and encoding polynucleotides so as to be able to use the claimed invention. Applicants have characterized the polypeptide of SEQ ID NO:2 as a

retinoic acid receptor. The functions and utilities of retinoic acid receptors are well established in the art and specifically recited in the specification. Retinoic acid receptors have substantial, real world uses and have been associated with specific disorders and are well known to be useful targets for human therapeutics. Thus, contrary to the Examiner's assertion, a functional nexus has been demonstrated between the protein of the instant application and human therapeutics.

For example, the following functions and utilities of retinoic acid receptors are specifically recited in the background section of the specification, particular in the section of the background entitled "Retinoic Acids and Retinoic Acid Receptors" on pages 3-5. Retinoids, or vitamin A metabolites/derivatives, have been determined to play essential roles in many aspects of development, metabolism and reproduction in vertebrates (p. 3, lines 19-21). Retinoic acid recptors modulate ligand-dependent gene expression by interacting as RXR/RAR heterodimers or RXR homodimers on specific target gene DNA sequences known as hormone response elements. In addition to their role in retinoid signalling, RXRs also serve as heterodimeric partners of nuclear receptors for vitamin D, thyroid hormone, and peroxisome proliferators (p. 3, lines 24-29).

Retinoids are essential for normal growth, vision, tissue homeostasis, reproduction and overall survival. Retinoids have been shown to be vital to the maintenance of skin homeostasis and barrier function in mammals. Retinoids are also apparently crucial during embryogenesis, since offspring of dams with vitamin A deficiency (VAD) exhibit a number of developmental defects. With the exceptions of those on vision and spermatogenesis in mammals, most of the effects generated by VAD in animals and their fetuses can be prevented and/or reversed by retinoic acid (RA) administration. The dramatic teratogenic effects of maternal RA administration on mammalian embryos, and the marked effects of topical administration of retinoids on embryonic development of vertebrates and limb regeneration in amphibians, have contributed to the notion that RA may have critical roles in morphogenesis and organogenesis (p. 2, 1st paragraph).

Retinoic acid receptors are the critical factors in tissue differentiation and development. They are up-regulated in rapidly dividing cells and tumors. retinoic acid receptors play an important role in lymphocyte activation. Synthetic antagonists of retinoic acid receptors can inhibit delayed type hypersensitivity (DTH). Growth factors and carotene regulate RXR

expression levels. For example, granulocyte macrophage colony-stimulating factor induces retinoic acid receptors in myeloid leukemia cells (p. 5, 2nd full paragraph).

Retinoic acid receptor gene rearrangements are the primary causes of some types of leukemia and provide a convenient genetic marker for malignant cell lines. A number of retinoic acid derivatives are used in treatment of myelodysplastic disorders. They are designed to bind and activate RXRs. Beta-carotene can prevent skin tumor formation in mouse models. N-(4-hydroxyphenyl)retinamide can delay onset of dysplasia in bronchi. Different chemopreventive drugs can be designed to target individual retinoic receptors. The sequences provided by the present invention may be used to design high affinity chemopreventive compounds (p. 5, last paragraph).

Such functions are quite specific for retinoic acid receptors and differentiate them from other proteins, including other nuclear hormone receptors. As such, these functions are specific enough to define a use for novel retinoic acid receptors and encoding nucleic acid molecules in the drug discovery process and to enable one of ordinary skill in the art to use the claimed invention without undue experimentation.

Thus, it is clear that the disclosure of novel nuclear hormone receptors, particularly novel retinoic acid receptors, satisfies a need in the art by providing important new compositions that are useful towards the prevention, diagnosis, and treatment of developmental, metabolic, and reproductive disorders, as well as various types of cancer, among other disorders. Consequently, one of ordinary skill in the art would recognize that novel nuclear hormone receptors, particularly novel retinoic acid receptors, and encoding nucleic acid molecules, have substantial, "real world" uses that meet the requirements of 35 U.S.C.§101.

Thus, there is overwhelming evidence in the art to support the utility of novel nuclear hormone receptors, particularly novel retinoic acid receptors, and encoding nucleic acid molecules. Not all nucleic acid molecules, and actually a very limited number, of the 3 billion bases that make up the human genome will encode a protein for these and the other disclosed uses. These uses are quite specific for the nuclear hormone receptor family of proteins, and each is a specific composition of matter having substantial, specific and credible uses that the vast majority of other isolated nucleic acid molecules do not possess.

By placing a new member of the nuclear hormone receptor family, particularly a novel retinoic acid receptor, into the public domain through the patenting process, the present invention

is not only a clear advancement over the prior art (a newly discovered protein/gene) but also enables significant advancement in medicine and further discovery. The Utility requirement cannot be used to contradict the reasons for the patent system, i.e., to encourage early disclosures of inventions so that others can benefit from, improve upon, and further develop such inventions. This is particularly important in medicine, wherein early disclosure of key inventions (such as new nuclear hormone receptors and encoding nucleic acid molecules) is needed to facilitate the early development of new therapies and diagnostics to treat illnesses.

The grant of a patent to the claimed isolated nucleic acid molecule and the resultant disclosure of the nucleic acid and protein sequences to the public will certainly shorten the process for medical researchers to discover other novel uses for the present nucleic acid molecules which encode nuclear hormone receptors. One example disclosed in the specification is that the present nucleic acid molecules can be used to produce protein targets for identifying agents that bind to the protein targets and modulate protein function. Such agents that bind to a protein target and modulate cellular processes such as signal transduction can subsequently be developed and refined for use in mammalian therapeutic applications. All of this later discovery and refinement will be done using the presently claimed material. These uses are clearly commercial and substantial uses that are specific for a very limited number of proteins/nucleic acid molecules.

In addition to serving as targets for developing molecular probes and therapeutic agents, the disclosed uses of the claimed nucleic acid molecules as probes, primers, and chemical intermediates, particularly in biological assays, is sufficient to satisfy the requirements of 35 USC §101 and §112. The claimed invention is directed to nucleic acid sequences, such as SEQ ID NOS:1 and 3, that encode a nuclear hormone receptor with a specified amino acid sequence (SEQ ID NO:2). Exemplary uses of the nucleic acid sequences are clearly recited in the specification on, for example, pages 42-61. Among the examples, the nucleic acid molecules are useful as hybridization probes for messenger RNA molecules, transcript/cDNA molecules, genomic DNA, and variants thereof. An expression vector comprising the nucleic acid sequences can be constructed that expresses the nuclear hormone receptor. Such uses are specific for the claimed nucleic acid molecules, and the products of such uses will be clearly different (and hence specific for the claimed molecules) than what would be produced using a different nucleic acid molecule for the same purpose.

In view of law and fact, the utility standard interpreted by the USPTO guidelines is too high. The commercial value of previously unidentified members of the nuclear hormone receptor family, particularly novel retinoic acid receptors, members of which are well known in the art to be commercially valuable drug targets, should be sufficient to satisfy the utility requirement. Therefore, applicants respectfully request that the Examiner withdraw the rejections.

Conclusions

Claims 4, 8-9, and 24-29 remain pending.

In view of the above remarks, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the rejections. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is invited to call the undersigned agent at (240) 453-3812 should the Examiner believe a telephone interview would advance prosecution of the application.

Respectfully submitted,

CELERA GENOMICS

By: _____

Justin D. Karjala, Reg No. 43,704

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Celera Genomics Corporation
45 West Gude Drive, C2-4#20
Rockville, MD 20850
Tel: 240-453-3812
Fax: 240-453-3084